

REMARKS

Claims 1, 2, 10-13 and 15-25 are now pending in the application.

Claim 1 is amended. Support is found in the original specification as filed, including page 6, lines 1-33.

Claims 3-6, 8 and 9 are cancelled without prejudice.

Claim 10 is amended to recite “silica particles.” Support is found in the original specification as filed, including page 10, lines 24-34.

Claims 19-24 are new claims depending from Claim 1 directly or indirectly. The claims are supported by the originally-filed specification. Illustratively, support for the claims can be found in the specification as filed as shown below:

Claim	Exemplary Support
Claim 19	Page 3, Lines 1-6 and original Claim 1
Claim 20	Page 3, Lines 1-6 and original Claim 1
Claim 21	Page 3, Lines 1-6 and original Claim 1
Claim 22	Page 3, Lines 10-11 and original Claim 1
Claim 23	Page 7, Lines 6-13
Claim 24	Page 7, Lines 6-13 and Page 9, Lines 13-24

Claim 25 is a new independent claim directed to a TDS comprising an aminotetralin compound which finds support from, for example, original Claim 1 and page 6, lines 1-8 of the originally-filed specification.

These claim amendments are made solely to further prosecution and Applicant reserves the right to pursue the claims in their non-amended form in one or more continuation applications. No new matter is added, and no change in inventorship is believed to occur, as a result of any amendment herein.

RESPONSE TO OFFICE ACTION DATED 24 JUNE 2009

1. Objection to Specification

The specification stands objected to for the following informalities: oxybutynin (as oxybutynine) is allegedly misspelled.

Oxybutynine is a known synonym of oxybutynin; it is not misspelled. Applicant encloses with the present amendment a listing of known synonyms of oxybutynin as evidenced by The

Merck Index, Thirteenth Edition (2001) “7024. Oxybutynin” Whitehouse Station, NJ: Merck & Co., Inc., pg. 1245 Therefore, reconsideration and withdrawal of this objection are respectfully requested.

2. Rejection Under 35 U.S.C. § 112

Claims 1–5, 8, 10–13 and 15–18 stand rejected for allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph. The Examiner objects to the term “amine functional drug”. However, the Examiner states: “The specification discloses chemicals, such as oxybutynin, rotigotine, fesoterodine, fentanyl, aminotetralin, and silica which meet the written description and enablement provisions of 35 USC 112, first paragraph.” (Office Action, p. 3)

Claim 1 is amended herein to recite “an amine-functional drug selected from the group consisting of fentanyl and oxybutynin” to further expedite prosecution. Support is found in the original specification as filed, for example page 6, lines 1–33. Applicant submits that the original specification demonstrates possession of the claimed subject matter and Claim 1 complies with the requirement of 35 U.S.C. §112, first paragraph.

Claim 10 is amended herein to recite “the self-adhesive matrix is free of silica particles that can absorb salts of the amine functional drug at the TDS/skin interface” to further expedite prosecution. Support is found in the original specification as filed, for example page 10, lines 24–34. Applicant submits that original specification demonstrates possession of the claimed subject matter and Claim 10 complies with the requirement of 35 U.S.C. §112, first paragraph.

New Claim 25 recites “an amine-functional drug selected from an aminotetralin compound” and thus also meets the written description and enablement provisions of 35 U.S.C. §112.

The §112 rejection on Claims 3 and 4 is rendered moot in view of the amendment cancelling the claims.

Therefore, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

3. Rejection Under 35 U.S.C. § 103 – D’Angelo, Mueller & Nugroho

Claims 1–6, 10, 11 and 15–18 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over D’Angelo et al. (U.S. Patent No. 5,932,240, herein “D’Angelo”) in view of Mueller et al. (WO99/49852, herein “Mueller”) as evidenced by Nugroho *et al.* (2004). The § 103 rejection on Claims 3–6 is rendered moot in view of amendment cancelling the claims. The § 103 rejection on the remaining claims is respectfully traversed because the alleged combination of these documents fails to meet all the criteria necessary to establish a *prima facie* presumption of obviousness for at least the reasons below.

First, the combined documents fail to provide for all of the claimed features.

Second, these documents fail to provide an apparent reason to combine their respective features and further include the missing elements necessary to recreate a TDS in the fashion claimed by Applicant.

Third, these documents fail to provide a reasonable expectation of success in modifying aspects of their disclosures as necessary to recreate Applicant’s claims.

3.1 The proposed combination of D’Angelo and Mueller does not teach all of Applicant’s claimed features.

To establish *prima facie* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The alleged combination of D’Angelo and Mueller fails to disclose all claimed features including:

- (1) an amine-functional drug selected from the group consisting of fentanyl and oxybutynin,
- (2) microreservoirs themselves,
- (3) microreservoirs within a self-adhesive matrix,
- (4) microreservoirs having a maximum diameter less than the thickness of the matrix, and
- (5) the matrix being permeable to an amine-functional drug in free base form, and the self-adhesive matrix is substantially impermeable to the amine functional drug in protonated form.

Independent Claim 1, as amended herein, is recites a TDS comprising a self-adhesive matrix containing a self-adhesive polymer and microreservoirs containing an amine-functional drug selected from the group consisting of fentanyl and oxybutynin,

wherein the microreservoirs are within the self-adhesive matrix and have a maximum diameter less than the thickness of the self-adhesive matrix; and

wherein the self-adhesive matrix is permeable to the amine-functional drug in free base form, and the self-adhesive matrix is substantially impermeable to the amine functional drug in protonated form.

(1) No teaching or suggestion of “fentanyl and oxybutynin”

The alleged combination of D'Angelo and Mueller fails to teach a transdermal drug delivery system for fentanyl and oxybutynin. The Examiner admits at page 11, lines 15-17 states that D'Angelo “does not teach the specific instantly claimed aminotetralin compound or silicone pressure adhesive.” This deficiency is not cured by Mueller since it describes neither fentanyl nor oxybutynin. Furthermore, the alleged combination fails to provide any guidance which would lead to selection of the claimed active compounds, *i.e.*, fentanyl and oxybutynin, for transdermal delivery systems having the same or similar construction as that of the claimed TDS.

(2) No teaching or suggestion of “microreservoirs” as defined in Claim 1

D'Angelo at Col. 4, lines 56-60 states: “The unit dose reservoirs of the assembly may be impressed or molded into the polymeric and impregnated materials or they may be formed by sealing the peripheries of impervious material layers to form pouches which, upon loading through openings, will become drug reservoirs.” (emphasis added) These “pouches” or “medicament/drug reservoirs” are filled with unit doses of the drug hydrogel. The microcapsules 8 in D'Angelo expressly span the matrix 18 as they are attached to each of the tear strip 5 and the permeable membrane 13 by microcapsule adhesive 19.

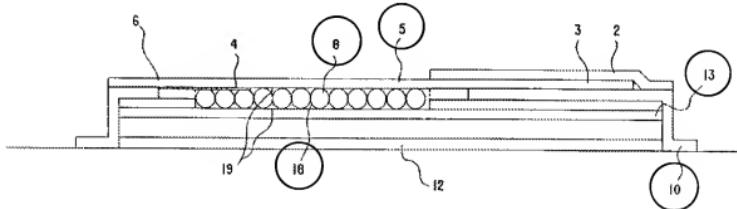
These components of D'Angelo should not be confused with the “microreservoirs” as defined in Claim 1 which are particulate, spatially and functionally separate compartments containing pure drug or a mixture of drugs. The microreservoirs of the present invention are small enough such that those separate compartments can be dispersed within a self-adhesive

matrix. Apparently, D'Angelo describes a structure different from microreservoirs of the invention and Mueller is silent with respect to such microreservoirs. Thus, the proposed combination fails to provide microreservoirs as defined in the claims of this application.

(3) No teaching or suggestion of a "self-adhesive matrix containing microreservoirs"

The acrylate adhesive border **10** of D'Angelo does not equal a self-adhesive matrix containing microreservoirs of the present invention. As noted in the Office Action, D'Angelo states that the drug hydrogel is in "major openings in the layer to be applied to the skin". According to D'Angelo, these "openings" are covered with Cotran® 9710, a micro-porous polyethylene. This is not an acrylate adhesive. In the same paragraph, D'Angelo states: "The patch was adhered to the shaved skin by the 3M Cotran® 9872 acrylate adhesives..." (emphasis added). That it, the D'Angelo "pouches" or "medicament/drug reservoirs" are not within the acrylate adhesive border of D'Angelo.

As can be seen from D'Angelo Fig. 2 below, the hydrogel matrix **18** and microencapsulated medicament **8** of D'Angelo are sandwiched between the tear strip **5** and the permeable membrane **13**. D'Angelo uses an adhesive border **10** to attach the transdermal assembly to the skin, so the logical and straightforward placement for a silicone pressure sensitive adhesive in the alleged combination of D'Anglelo and Mueller is at the adhesive border **10**. The adhesive border **10** is the outer border of the assembly for attaching the assembly to skin.



The matrix **18**, the microcapsules **8** and the adhesive border **10** are not one in the same. D'Angelo provides separate adhesive and drug portions of the assembly while Mueller provides a dispersion of drug in adhesive. These are dissimilar features and the present rejection has failed to reconcile how D'Angelo's matrix **18**, microcapsules **8** and adhesive border **10** would be

redesigned to accommodate the dispersion of drug in adhesive from Mueller and still function. The combination alleged by the Examiner consequently fails to teach or suggest microreservoirs within a self-adhesive matrix as defined in Claim 1.

(4) No teaching or suggestion of “microreservoirs having a maximum diameter less than the thickness of the matrix”

Similar to the argument above, the “microencapsulations” of the drug active (*i.e.* the insulin encapsulated capsules of 1 to 150 microns diameter) are not the same as the microreservoirs of the present invention. Even if the D’Angelo “microencapsulations” were the same as the microreservoirs of the present invention, the above statement contains a *non sequitur*. D’Angelo does not provide any guidance or suggestion that could lead to microreservoirs having a maximum diameter less than the thickness of the self-adhesive matrix. More importantly, microreservoirs of the present invention are undesirable in D’Angelo’s transdermal system because such microreservoirs make the tear-and release mechanism inoperable. Furthermore, D’Angelo fails to teach microreservoirs within a “self-adhesive matrix” because there is no “self-adhesive matrix” in D’Angelo’s transdermal systems. The only adhesive in D’Angelo is at the acrylate adhesive border **10**, which is used to adhere the D’Angelo patch to the skin.

Unlike the present invention, the D’Angelo microencapsulated medicament **8** therefore necessarily spans the matrix **18** as they are attached to each of the tear strip **5** and the permeable membrane **13** by microcapsule adhesive **19**. Activation of the unit dose includes pulling back the tear strip **5** so that the frangible medicament capsules are ruptured to release medicament which diffuses through the permeable membrane **13**. If the microencapsulated medicament “spans the matrix”, their diameter must be at least equal to the thickness of the matrix – whether the microcapsules are 1 micron or 150 microns.

Thus, contrary to the Office Action’s assertion, one of ordinary skill would be demotivated by the teaching of D’Angelo because

(1) D’Angelo requires its microencapsulated medicament to be “adhered to [not less than] the bottom of a tear strip **5** and to the top of a permeable membrane **13** (col. 8, lines 3–6); and

(2) D'Angelo emphasizes a means for disrupting the microcapsules, which in some embodiments is achieved by pulling back the tear strip, to which the "frangible" microcapsules are adhered (col. 8, lines 34–39). One of ordinary skill would be de-motivated, by the teaching of D'Angelo regarding the significance of the disruption mechanism, to reduce the diameter of the microcapsules, such that the microcapsules no longer contact the layers above and below the matrix in which they are embedded.

Therefore, D'Angelo not only fails to disclose, but indeed teaches away from, (a) a self adhesive matrix layer containing microreservoirs of (2) diameter smaller than the thickness of the matrix layer. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. MPEP 2145.X.D.3, citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

(5) No teaching or suggestion of a self-adhesive matrix having the claimed permeability characteristics

The microcapsules **8** in D'Angelo separate the drug from the gel-like matrix **18**, which is an entirely different scenario than the dispersion of free base rotigotine and silicone adhesive in Mueller. Nothing in either document dispository indicates whether the gel-like matrix **18** would be permeable to fentanyl and oxybutynin in free base form and is substantially impermeable to fentanyl and oxybutynin in protonated form. Obviousness cannot be predicated on what is unknown and unappreciated. Thus, the combination fails to provide this facet of Claim 1.

As illustrated above, the alleged combination of D'Angelo and Mueller fails to provide for all of the claimed features and cannot establish a *prima facie* presumption of obviousness.

3.2 There is no apparent reason to combine D'Angelo and Mueller in a fashion that recreates Applicant's claims.

For a finding of obviousness predicated on a combination of documents, there must be an apparent reason for a skilled artisan to make the alleged combination. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007) (obviousness includes determining whether there was an apparent reason to combine the known elements in the fashion claimed). MPEP §

2143 states that “[t]he key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious,” which should be made explicit and must be anchored by a rational underpinning, as directed by *KSR Int'l Co. v. Teleflex Inc.* This burden is not met in the present rejection based on D'Angelo in view of Mueller.

Applicant submits that there is no reason either in the references or the general knowledge in the art to combine and modify the cited references to arrive at Claim 1. Further, no reason has been articulated in the Office Action to embed microreservoirs within the self-adhesive border as opposed to a gel matrix layer as disclosed by D'Angelo. Even if one of ordinary skill in the art would have been motivated to make such a combination and modification (which is not admitted herein), that combination and modification would not have provided microreservoirs within a self-adhesive matrix, as required by Claim 1 for at least the following reasons:

(1) ***Independent components provide no reason for combination & modification:*** In contrast to the present invention, D'Angelo mentions an acrylate adhesive and microcapsules as independent components of a patch. This is not sufficient to establish a *prima facie* case of obviousness. Under *KSR, supra* (emphasis added), “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. ... [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.”

The present Action's identification of a reference with microcapsules and a self-adhesive acrylate, each discussed independently in the reference, is exactly the type of hindsight reconstruction warned against in *KSR*.

(2) ***Combination & modification yields a patch unsatisfactory for its intended purpose:*** The Office Action fails to address Applicant's argument that a modification of D'Angelo to reduce the size of the microcapsules (to have a diameter that is less than the thickness of the

layer wherein they are embedded.), far from being a routine modification, would render the patch of D'Angelo unsatisfactory for its intended purpose. “If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.” MPEP 2143.01.V, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). If microcapsule diameter were reduced so that the microcapsules no longer adhered to the tear-off strip, the patch of D'Angelo would no longer function as intended.

(3) ***Combination & modification would change the principle of operation:*** The Office Action also fails to address Applicant's argument that, alternatively, a modification of D'Angelo to reduce the size of the microcapsules would change the principle of operation of the D'Angelo patch. “If the proposed modification ... would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.” MPEP 2143.01.VI, citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). If microcapsule diameter were reduced so that the microcapsules no longer adhered to the tear-off strip, the principle of operation of D'Angelo would be changed, indeed lost.

(4) ***Generic D'Angelo disclosure:*** Applicant maintains that nothing in D'Angelo would motivate one of ordinary skill to select fentanyl or oxybutynin free base over any other pharmacological agent. In fact, the exemplary list of drugs is prefaced with the statement that “almost any drug, to some degree, can be administered transdermally” (D'Angelo, col. 1, lines 58–59).

Thus, nothing in D'Angelo, Mueller or the art suggests that it would be beneficial for microreservoirs to have a maximum diameter less than the thickness of the matrix layer (in D'Angelo a gel matrix layer, not a self-adhesive matrix layer) in which they are embedded.

3.3 There is no reasonable expectation of successfully combining D'Angelo and Mueller in a fashion that recreates Applicant's claims.

When formulating a *prima facie* presumption of obviousness, a reasonable expectation or predictability of success is required, as noted in MPEP § 2143.02: “The mere fact that references can be combined or modified does not render the resultant combination obvious unless the

results would have been predictable to one of ordinary skill in the art." And see *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143, 148 (C.C.P.A. 1976) (stating that there must be a showing of a reasonable expectation of success and the alleged combination cannot be said to be "inherently" successful).

In this case, there is no basis for such predictability found in D'Angelo and Mueller or provided from the general knowledge in the art.

First, there is no guidance provided to make a transdermal assembly from the alleged combination having a matrix permeable to the free base of fentanyl or oxybutynin and substantially impermeable to the protonated form of fentanyl or oxybutynin, as found in Claim 1. For example, the hydrogel matrix **18** of D'Angelo likely contains enough water to produce the salt form of an amine functional drug, such as fentanyl or oxybutynin; see the present specification as filed on page 7, line 24 to page 8, line 9 where it is noted that less water results in less salt form of the amine functional drug. Thus, the alleged transdermal assembly would have a matrix that is likely permeable to the protonated form of fentanyl or oxybutynin, which is antithetical to Claim 1.

Second, there is also no reasonable expectation of success in making a transdermal assembly from the alleged combination where the microcapsules have a maximum diameter that is less than the thickness of the matrix. D'Angelo teaches that the microcapsules are required to be attached to both the bottom of the tear strip **5** and to the top of the permeable membrane **13** using the microcapsule adhesive **19** in order for the assembly to function regardless of the diameter of the microcapsules. In other words, the matrix **18** layer thickness is dependent on the diameter of the microcapsules **8**. There is no alternative way provided in the cited documents to replace the necessary tear off and rupture of the microcapsules in order to activate the assembly and the Office Action fails to provide an alternative means based on the general knowledge in the art and indicate how and why it would function in lieu of the tear off. Thus, a person of ordinary skill in the art would not reasonably predict that modifying the diameter of the microcapsules to be less than the matrix thickness would be successful.

As illustrated, the alleged combination of D'Angelo and Mueller fails to provide a reasonable expectation of success. Therfore, a presumption of *prima facie* obviousness has not been established.

3.4 Rejection under 35 U.S.C. §103(a): Conclusion

A presumption of *prima facie* obviousness has not been established over the alleged combination of D'Angelo and Mueller at least because:

- (1) The alleged combination fails to provide for all of the elements of Claim 1;
- (2) There is no apparent reason either in the references or the general knowledge in the art to combine and modify the references to include the missing subject matter in the fashioned claimed by Claim 1; and/or
- (3) No reasonable expectation of success is provided by the alleged combination or the general art to recreate Claim 1.

Notwithstanding the Examiner's remarks with respect to the subject matter of dependent Claims 2, 10, 11 and 15-18, these claims each embody all the limitations of Claim 1 from which they depend or which they reference, and are therefore nonobvious at least for the same reasons that Claim 1 is nonobvious. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. MPEP 2143.03. Reconsideration and withdrawal of the present rejection under 35 U.S.C. §103(a) are respectfully requested.

4. Rejection Under 35 U.S.C. § 103 – D'Angelo, Mueller & Quan

Claims 8 and 9 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over D'Angelo et al. (U.S. Patent No. 5,932,240, herein "D'Angelo") in view of Mueller et al. (WO99/49852, herein "Mueller") and further in view of Quan et al. (U.S. Patent No. 5,834,010).

The rejection is rendered moot in view of the amendment cancelling Claims 8 and 9. Reconsideration and withdrawal of the present rejection under 35 U.S.C. §103(a) are respectfully requested.

5. Rejection Under 35 U.S.C. § 103 – D'Angelo, Mueller, Pfister & Nugroho

Claims 12 and 13 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over D'Angelo et al. (U.S. Patent No. 5,932,240, herein "D'Angelo") in view of Mueller et al. (WO99/49852, herein "Mueller") and further in view of Pfister et al. (U.S. Patent No. 5,232,702) and as evidenced by Nugroho et al. This rejection is respectfully traversed.

The shortcomings of the combination of the D'Angelo and Mueller documents are illustrated in the preceding sections. Pfister is further added to the combination for allegedly disclosing a blend of high tack and medium tack silicone pressure sensitive adhesives. However, Pfister fails to overcome the aforementioned deficiencies of the D'Angelo and Mueller combination and the collective disclosures of these three documents fail to provide for all of the claimed features and cannot establish a presumption of *prima facie* case obviousness. Moreover, these documents fail to provide a reasonable expectation of success in modifying aspects of their disclosures as would be necessary to recreate Applicant's claims. These documents further fail to provide an apparent reason to combine their respective features and include the missing elements in order recreate a TDS in the fashion claimed by Applicant.

Reconsideration and withdrawal of the present rejection under 35 U.S.C. §103(a) are respectfully requested.

6. Conclusion

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the Application is in condition for allowance.

If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number listed below.